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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,499	05/04/2001	Herman Waldmann	1324.028	8699

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Mark. S. Cohen
EITAN, PEARL, LATZER & COHEN ZEDEK, LLP
10 Rockfeller Plaza
Suite 1001
New York, NY 10020

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,499	WALDMANN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 6/1/05.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 64,68-95,105-108,110 and 111 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 64,68-95,105-108,110 and 111 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Applicants' Responses, filed 6/1/05 and 1/13/05 have been entered. The Amendment, filed 6/1/05 is responsive the Notice of Non-Compliant Amendment, mailed 4/1/05. Claims 64, 68-71, 83-86, 89-95 are amended; claims 110-111 are newly added; claims 64, 68-95, 105-108, 110, 111 are pending and under current examination.

The Fairchild Declaration has been considered.

Claim Objections

Claim 110 objected to because of the following informalities: the claim does not end in a period. Appropriate correction is required.

Specification

The prior objection to the specification is maintained. Applicants have submitted a replacement specification that comprises the text of the parent published PCT reformatted in accordance with current USPTO practice. However, the substitute specification filed 2/12/03 has not been entered because it does not conform to 37 CFR 1.125(b) because: Applicants have not provided a copy of the specification excluding the claims, as well as a marked up version of the specification showing all the changes (including the matter being added to and the matter being deleted from) to the specification of record. See also MPEP §608.01(q).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 64, 68-95, 105-108, 110 and newly added claim 11 is *maintained* under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a long-term culture of immature dendritic cells wherein the method comprises culturing mouse or human ES cells *in vitro* in the presence of IL-3 [and optionally, murine GM-CSF] to bring about differentiation of the ES cells into immature dendritic cells and stimulating the maturation of the immature dendritic cells, does not reasonably provide enablement for methods for producing long-term cultures of immature dendritic cells utilizing any population of ES cells, for the breadth claimed, culturing the ES cells in the presence of any cytokine or combination of cytokines to bring about the differentiation of the ES cells into immature dendritic cells to produce a long-term culture of immature dendritic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants traverse and disagree with the Examiner's assertion and argue that one of skill in the art could make any mouse or human dendritic cell from any mouse and human ES cell. Applicants provide the Fairchild declaration as evidence for this argument. See pp. 8-9 of Applicants' Response.

In response to this argument, it is noted that Applicants only argue the production of mouse or human dendritic cells from mouse/human ES cells. The claims are far broader than this, encompassing any dendritic cell from any ES cell. There is no guidance provided by the instant specification for enablement of the

breadth of species of ES cells, and culture conditions required, to produce immature dendritic cells, to enable the claimed invention. The specification provides a single working example, by culturing the ESF116 mouse cell line with a particular cytokine, murine IL-3. The state of the art of directing differentiation of ES cells to a particular cell type is found to be exceedingly unpredictable, showing that using different combinations of cytokines, only GM-CSF and IL-3 have found to have the capacity to support DC development.

The Fairchild declaration states that the Examiner is incorrect in the basis of this rejection because the disclosure teaches one of skill in the art how to make dendritic cells from mouse or human ES cells, and that ES cells derived from at least three mouse strains were effective in differentiating into dendritic cells. Applicants argue that they have extended their work to several other mouse ES cells, each of which have behaved identically with respect to the production of dendritic cells. Applicants provide Cheng *et al.* to show the successful use of a commercially available mouse ES cell line derived from 129 mice (R1) for the generation of dendritic cells, according to Applicants' published protocols. See pages 1-2 of the Declaration. The declaration further states that since at least 3 mouse ES cell lines were effective in producing a long-term culture of immature dendritic cells, by culturing the ES cells in the presence of IL-3, one of skill in the art would be able to practice the invention without undue experimentation. See page 3, #6 of the Declaration. Applicants argue similarly in their Response, reiterating the Declaration, that Cheng show the successful use of a commercially available mouse ES cell to generate DCs, according to the teachings of the invention, and that the application demonstrates the production of long-term cultures of immature dendritic cells utilizing three mouse ES cell lines in a culture comprising IL-3 (p. 9 of the Response).

These arguments are partially persuasive with regard to culturing mouse ES cells in IL-3. However, they are not found to be persuasive for the breadth of the

claims, with regard to culturing with any cytokine. The declaration states that they were cultured in the presence of IL-3, however, this fails to support the breadth of the claims comprising culturing any ES cell with any cytokine. Cheng, cited by the Declaration, has been considered, and is persuasive with regard to mouse ES cells.

The Declaration further states that there is a significant conservation between the developmental processes of mouse and human, with regard to hematopoeisis, therefore, based upon the disclosed methods, one of skill in the art would be able to practice the claimed invention, without undue experimentation (see #7 of the Declaration). The Declaration states that derivation of dendritic cells from human ES cells was demonstrated by Zhan *et al.*, who generated a broad range of hematopoietic cell types from human ES cells, including dendritic cells. They state that they adapted a protocol previously used for mice, citing Fairchild *et al.*, and that their method corresponds to the method of the subject application. Further, the Declaration points to Zhan *et al.* and states that they apply the protocol using IL-3, as claimed in the instant application, and then, to broaden the range of leukocytes obtained, added a number of other growth factors. They teach the addition of IL-4 to the culture medium to enhance possible maturation of lymphoid cells and dendritic cells. Thus, the Declaration concludes that the claimed invention is enabled. See #9-10 of the Declaration. Applicants argue similarly, that Zhan generated a broad range of hematopoietic cell types from human ES cells, including dendritic cells, and that Zhan *et al.* used the protocol developed by Fairchild *et al.*, which corresponds to the method of the instant application. See p. 10 of the Response.

These arguments have been considered, and are found to be partially persuasive. It is noted that Applicants are arguing only with respect to mouse and human ES cells (and the production of immature dendritic cells therefrom). The breadth of the claim is to any ES cell, from any species, to produce any long term cultured, immature dendritic cell. Zhan *et al.* has been considered, and is

persuasive with regard to human ES cells. Zhan teach culturing the human ES cell line, H1, in a medium containing IL-3 and GM-CSF, and to enhance the possible maturation of DCs, they added IL-4. See p. 164-65, bridging ¶. The resultant cells were then isolated by particular antibodies (see p. 165, Flow Cytometric Analysis, and Table). Zhan teach the expression of 21 surface markers on the differentiated cells, for example CD83, which is a marker for mature DCs, and CD40 which is expressed in DCs. They teach that dendritic cells were seen in the cultures (see p. 170).

Applicants argue that one of skill in the art would enable the claimed invention without undue experimentation to any embryonic stem cell population, namely ES cells from additional mice strains, as well as mammals, including human. (Emphasis added, see p. 4, 1st ¶ of the Response). This is not persuasive because the specification and the Declaration, with supporting references, only provide an enabling disclosure for culturing mouse or human ES cells in the presence of IL-3 to produce immature dendritic cells. There is no guidance and the arguments do not overcome the unpredictability in culturing any ES cell with any cytokine to produce immature dendritic cells.

Accordingly, in view of the quantity of experimentation necessary for the production of long-term cultures of immature dendritic cells by culturing any ES cells with any cytokine [or combination thereof], the lack of guidance, teachings and examples provided by the specification for the production of long-term cultures of immature dendritic cells from any ES cells with any cytokine, other than the mouse or human ES cell lines with IL-3 [and optionally murine GM-CSF], as well as the unpredictable state of the art with regard to the availability of ES cells lines capable of supporting DC development, and the requirement for IL-3 for differentiation, it would have required undue experimentation for one skilled in the art to make and/or use the claimed long-term cultures of dendritic cells and methods of making the same.

Claim Rejections - 35 USC § 112

Claim 110 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by Applicants' amendment, adding this claim.

Claim 110 recites the limitation "the method of claim 64" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
Thaian N. Ton
Patent Examiner
Group 1632

Joel Weitekamp
HU1632